

DEVELOPMENT AND VALIDATION OF A MODIFIED FULL AGE SPECTRUM CREATININE-BASED EQUATION TO ESTIMATE GLOMERULAR FILTRATION RATE

TO THE EDITOR: Pottel and colleagues (1) have developed a new equation to estimate glomerular filtration rate (GFR) across the full age spectrum. One major improvement is that this equation, known as the European Kidney Function Consortium (EKFC) equation, smooths estimated GFR (eGFR) across the transition from adolescence to adulthood. In adults, the main conceptual difference compared with previous equations is a threshold for the age parameter using a coefficient of $0.990^{(\text{Age} - 40)}$ only in patients older than 40 years. Indeed, this equation substantially improves GFR estimation in young adults compared with the Chronic Kidney Disease Epidemiology Collaboration equation, which incorporates age for all adults (using a coefficient of 0.993^{Age}) and suffers from overestimation in those younger than 40 years.

Pottel and colleagues explain that this threshold is based on the established pattern of GFR variation with age, which is stable in young adults and decreases from the age of 40 years (2). However, we would like to clarify that the age factor in GFR estimation equations derived from serum creatinine (SCr) models variations in “non-GFR determinants” of SCr with age, particularly muscle mass (3). In other words, if muscle mass were stable with age, no age factor would be necessary for the equation to properly model variations of GFR with age. Therefore, the reason this age threshold of 40 years improves GFR estimation in young adults is not because “the EKFC model accounts for the age dependency of GFR”; instead, the fact that it improves estimation suggests that muscle mass is stable in young adults and that the EKFC model properly accounts for the age dependency of muscle mass.

In order to analyze the variation of muscle mass with age, we evaluated 2403 GFR measurement data sets (using urinary clearance of exogenous tracers) from 2008 to 2020 in White adult patients from our physiology unit (mean age, 51 years [SD, 15]; 57% men). We calculated urinary creatinine output from the average of the 6 fractionated urine samples collected during the procedure. Stability younger than age 40 years (with mean values of 15.7 and 10.3 mmol/24 h in men and women, respectively) was confirmed, explaining the improved performance of the EKFC equation in this age range. A statistical model assuming constant value until an age threshold and exponential decline thereafter showed that this surrogate of muscle mass started to decline at age 48 years with a rate of decrease estimated as $0.992^{(\text{Age} - 48)}$ in men and age 47 years with a rate of decrease estimated as $0.991^{(\text{Age} - 47)}$ in women.

Overall, should an age cutoff be forced into the equation, it should rely on dedicated studies establishing the age dependency of muscle mass and not that of GFR.

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Disclosures: Authors have reported no disclosures of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L21-0247.

doi:10.7326/L21-0247

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IN RESPONSE: The goal of eGFR equations is to predict measured GFR (mGFR). The age cutoff in the EKFC equation was chosen on the basis of dedicated studies establishing the age dependency of mGFR and the age/sex dependency of SCr. Indeed, mGFR in healthy participants was shown to be stable around 107 mL/min/1.73 m² until approximately age 40 years. It then starts to decline (1, 2) independent of how SCr evolves with age, which is entirely different (3). This difference in the SCr-age pattern compared with how mGFR evolves with age is the main reason why eGFR equations were developed separately for children and adults.

To make an equation for the complete age range, we “normalized” or “rescaled” SCr and used SCr/Q (with Q representing the sex- and age-specific median creatinine value in healthy persons) as an independent variable in the eGFR equation. Doing so allowed us to overcome the differences in SCr generation between both children and adults and men and women, which are probably due to differences in muscle mass. However, to simplify matters, we did not change the normalization constants (Q = 0.70 mg/dL for women and 0.90 mg/dL for men) for older adults. We integrated the increase in SCr with the observed decline in mGFR by introducing the age decline rate factor from the age of 40 years or older.

As Dr. Vidal-Petiot and colleagues state, the exponent to age in eGFR equations might also take into consideration the influence of muscle mass on SCr concentration. Decline in both estimating GFR and muscle mass could interfere in opposite ways, even if the interindividual variation of SCr due to muscle mass is probably very large. Still, from a pragmatic point of view, the EKFC equation performs better across the full age spectrum.

Moreover, for cystatin C, there is no need to “normalize” differently for children and adults, as shown from the Full Age Spectrum equation in which cystatin C was normalized by 0.82. Cystatin C for healthy participants does not vary with sex, but we and others noticed an increase with age in healthy populations. Thus, we switched the normalization factor from 0.82 to 0.95 for those older than 70 years (4, 5). Because cystatin C is not influenced by muscle mass, another mechanism must require the introduction of a decline rate factor for GFR after age 40 years; this mechanism is probably the physiologic decrease in mGFR.

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Disclosures: Disclosures can be viewed at
www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-4366.

doi:10.7326/L21-0248

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